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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,479	11/13/2003	Yoshihiko Yagi	02-333-A	8385

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EXAMINER

LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
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1648

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/712,479

Applicant(s)

YAGI ET AL.

Examiner

Zachariah Lucas

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 13 November 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6, 8-13, 15, 17-22, 24, 26-33, 35 and 37-40 is/are rejected.
- 7) ☒ Claim(s) 5, 7, 14, 16, 23, 25, 34, and 36 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

1. Currently, claims 1-40 are pending and under consideration.

#### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 9, 18, 27, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on methods of detecting RNA polymerase activity through the use of dyes that bind to double stranded RNA and which are excited at wavelengths between 475 and 495 nm and fluoresce at wavelengths between 518 and 542 nm. These claims are rejected because the claims do not specify the conditions under which the dyes have these excitation and fluorescing characteristics. In particular, it is noted that the application specifies that these wavelengths are characteristic to certain dyes "Under preferred assay conditions." Page 7. One of these dyes, the cyanine dye known and sold as PicoGreen® is disclosed in the application as having excitation/emission wavelengths (ex/em) within the claimed ranges. However, other teachings in the art indicate that the same dye has an ex/em of 502nm/523nm (Kricka, Ann Clin Biochem 39: 114-129 at 115. Thus, this reference teaches a different ex/em than that disclosed by the current application, indicating that the assay conditions may have an effect on the performance of the dyes. Because the claims do not specify under

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what conditions the required ex/em are to be found, the scope of the dyes being claimed is unclear.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 8-11, 17-20, 26-31, and 37-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to methods for the detection of RNA polymerase activity, or for the identification of inhibitors of such activity, wherein the methods involve continuous-monitoring of the enzymatic activity of the target RNA polymerase in the presence of a fluorescent dye capable of binding to double-stranded nucleic acids. It is noted that while claims 1-9 and 19-29 do not require the presence of the fluorescent dye in the reaction mixture to which the polymerase is added, because the claims are drawn to continuous read methods and require the measurement of the fluorescence of the reaction mixtures, the claims are interpreted as requiring the addition of the dye during the reaction of the polymerase with the reaction mixture, and its continuous presence in the mixture during the assay.

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The claims are rejected because there is insufficient support in the application for the use of the claimed methods for the detection of, or identification of inhibitors for, any RNA polymerase using any fluorescent dye capable of binding to double-stranded nucleic acids.

In support of the claimed methods, the application teaches a continuous read assay for the detection of HCV NS5B RNA-polymerase activity in the presence of the fluorescent cyanine dye PicoGreen®, and other such cyanine dyes in Examples 1 and 4. See, pages 10-11, and 14 of the application. Thus, the Applicant appears to have provided adequate written description for methods of the detection of NS5B activity and inhibitors.

The application also teaches that the use of the same dye can have different effects on the activity of a target polymerase. See e.g., page 8 (noting teachings in the art that the cyanine dye PicoGreen® was useful for the continuous monitoring of an E-coli DNA polymerase, but appeared to inhibit the enzymatic activity of an HIV DNA polymerase). The application further indicates that this demonstration in the art indicates uncertainty in the art by asserting that these teachings render “unexpected” the disclosed method of using a nearly identical continuous read method for the monitoring of HCV NS5B activity. *Id.* By identifying the disclosed method as unexpected, the application implicitly admits that the art surrounding the claimed invention is uncertain.

Where there is uncertainty in the art, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession. See, MPEP 2163 II.A.3(a). Further, the courts have indicated that the illustration of certain species of a claimed genus does not necessarily demonstrate possession of the genus, where there is “unpredictability in performance of certain species or

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subcombinations other than those specifically enumerated.” See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support). Thus, in situations where there is uncertainty in art as to the performance of different species from those specifically disclosed, such as in the present case, the Applicant must provide additional teachings to overcome this uncertainty.

Such additional teachings have not been provided in the present application. As indicated above, the Applicant has shown that various cyanine dyes may be used in the claimed methods for the detection of HCV NS5B activity. However, both the teachings in the application and in the art indicate that the utility of these dyes is not universal. Further, there is no demonstration that these dyes may be useful in methods for the detection of enzymatic activity by any RNA polymerase as is required by the present claims. In view of the teachings in the art regarding the uncertainty of the use of these dyes for the continuous monitoring or polymerase activity, the Applicant’s implicit admission of this uncertainty, and the provision of only a single instance where the dyes were found not to inhibit activity of an RNA polymerase, the limited descriptive support in the application are insufficient to demonstrate possession of the full scope of the claimed invention.

### ***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-4, 10-13, 19-22, 28, 30-33, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sutherland et al. (U.S. 5,049,490) in view of Toyoda et al. (U.S. 6,639,053).

These claims are directed to continuous read methods for the detection of, or for identification of modulators of, RNA polymerase activity comprising the steps of contacting an RNA polymerase with an oligonucleotide template, a reaction mixture, and a fluorescent dye capable of binding to double-stranded nucleic acids, and measuring the fluorescence of the mixture.

Sutherland teaches methods for the determination of a DNA polymerase activity comprising the steps of introducing the polymerase to a template, a reaction mixture, and to a fluorescent dye that binds to double-stranded nucleic acids. See, column 2, lines 16-20; and the paragraph spanning columns 2 and 3. The reference additionally teaches that the dye may be present in the reaction mixture either before or after the addition of the polymerase. See e.g., column 16, lines 55-68. However, the reference is primarily concerned with the methods as they relate to DNA polymerases, and does not teach or suggest the application of such methods with respect to RNA polymerases in general, or the HCV NS5B polymerase in specific.

Toyoda teaches a recombinant HCV NS5B polymerase. Abstract. The reference teaches that this RNA polymerase may be used in assays for screening for polymerase activity such that inhibitors of the activity may be identified. Columns 2-3. The reference teaches the screening for polymerase activity through the introduction of the polymerase to a template sequence, and to a reaction mixture. Claims 5 and 6; and column 5, lines 29-43. However, the reference does not teach continuous read assays.

From the teachings of the two references, it would have been obvious to those in the art that the continuous read assays of Sutherland would also be useful for the detection of HCV NS5B activity, and for the identification of inhibitors thereof.

8. Claims 29 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sutherland and Toyoda as applied to claims 1-4, 10-13, 19-22, 28, 30-33, and 39 above, and further in view of Diamond et al., U.S. 5,597,697. These claims are directed to the claimed methods wherein the method identify agonists of the target polymerase. The previously cited references do not teach or suggest these embodiments. However, the teachings of Diamond indicate that it would have been obvious to those in the art that a method for identifying inhibitors of a polymerase could also be used for the identification of agonists thereof. See e.g., claim 16. Thus, the limitations of claims 29 and 40 would have been obvious variations of the methods suggested by the previously cited references.

9. Claims 6, 15, 24, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sutherland and Toyoda as applied to claims 1-4, 10-13, 19-22, 28, 30-33, and 39 above, and further in view of Kinnunen et al. (U.S. 5,792,612). These claims further require the presence of large unilamellar vesicles in the reaction mixtures. The previously cited references do not teach the use of such vesicles.

However, Kinnunen teaches that the inclusion of unilamellar lipid liposomes (vesicles) increased by threefold the activity of polymerases in a PCR assay. Columns 5-6. It would therefore have been obvious to those of ordinary skill in the art to include such liposomes in the



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reaction mixture as described by the previously cited references so as to further improve the detection of polymerase activity by increasing the enzymes efficiency. The additional teachings of Kinnumem therefore render the additional limitation of claims 6, 15, 24, and 35 obvious.

### ***Conclusion***

10. No claims are allowed. Claims 5, 7, 14, 16, 23, 25, 34, and 36 are objected to as depending from rejected claims. The sequences of these claims appear to be free of the prior art.

11. It is noted that the application asserts on page 8 that Seville et al. (Biotechniques 21: 664, 666, 668, 670, 672) teaches that while the cyanine dye PicoGreen® was useful for the detection of enzymatic activity of E. coli DNA polymerase, no such detection was made for HIV reverse transcriptase (a viral polymerase), and concludes from this that the claimed method of using the dye to detect activity by viral RNA polymerase would have been unexpected to those in the art. The reference teaches that inclusion of the dye in the reaction composition did appear to inhibit the activity of HIV RT. Thus, the teachings of the reference would appear to support the application's assertion of unexpected results to the extent that the claims are limited to continuous-read methods wherein the continuous read limitation is performed by continuous measurement of the fluorescence of a non-symmetrical cyanine dye that binds to the double stranded RNA. I.e., the teachings of this reference appear to render the inventions of claims 8, 17, 26, and 37 non-obvious.

However, with respect to those claims that are not directed to embodiments wherein the dye is a cyanine dye as used in the Seville reference, the assertion of non-obviousness is not

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found persuasive. The showings of unexpected results must be commensurate with what is being claimed. See e.g., 716.02(d). In the present case, while the teachings in the application and the art indicate that a certain class of nucleic acid binding dyes may demonstrate unexpected results in certain embodiments of the claimed methods, there is no showing that these results would be unexpected with the use of any other dyes known in the art. Thus, while the teachings of Seville indicate non-obviousness of the claims identified in the paragraph above, the teachings of this reference are directed to a particular class of dyes, whereas the remaining claims in the application are generic to any fluorescent dye known in the art to bind to double stranded nucleic acids.

12. The following prior art references are made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons, and in view of the discussion of the teachings of Seville et al. above.

Kricka et al., *Ann Clin Biochem* 239: 114-29; and Haugland et al., U.S. 5,436,134. These references teach fluorescent unsymmetrical cyanine dyes that bind to double stranded nucleic acids. The references do not teach the use of such dyes for the measurement of RNA polymerase activity.

The following references each teach methods for the detection of activity of DNA or RNA polymerases: Diamond, U.S. 5,597,697; Malcolm et al., U.S. 2004/0142322; and Furfine et al., U.S. 2004/0170966. The references also teach the use of such assays for the identification of inhibitors of these enzymes. However, the references teach the use of different means of measuring the enzyme activities that through the use of the claimed dyes. Furfine indicates that the methods may be used for the detection of DNA and RNA polymerases, and for the identification of modulators of such enzymes. Abstract.

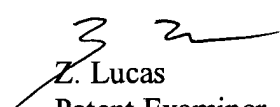
Singer et al., *Analytical Biochemistry*, 249: 228-38. This reference teaches dyes that bind to double stranded nucleic acids. Abstract. The reference also provides motivation for the preferential use of unsymmetrical cyanine dyes. See, carryover paragraph spanning pages 228 and 229, and first full paragraph page 229. The reference does not teach the use of such dyes for the measurement of RNA polymerase activity.

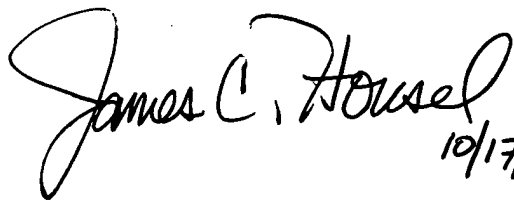
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13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
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10/17/05